



# Ductal adenocarcinoma of the pancreas and its variants - A clinicopathological study of 22 Tunisian patients

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## ABSTRACT

Background: Pancreatic ductal adenocarcinoma is an aggressive malignancy with a high mortality rate. It accounts for 85-90% of all pancreatic tumours. Aim: To provide an updated overview on clinicopathological features, treatment and outcome of ductal adenocarcinoma of the pancreas and its variants. Material and methods: We retrospectively reviewed 22 cases of ductal adenocarcinoma of the pancreas and its variants that were diagnosed at the pathology department of Mongi Slim hospital over a

fourteen-year period (2000- 2013). Results: Our study group included 16 men and 6 women (sex ratio M/F = 2.66) aged between 33 and 79 years (mean = 65 years). The presenting clinical symptoms were dominated by jaundice (n=21), followed by abdominal pain (n=18), altered general health (n=15), vomiting (n=3) and epigastralgia (n=3). Twenty patients underwent cephalic duodenopancreatectomy and two patients had total duodenopancreatectomy. Histopathological examination of the surgical specimen established the diagnosis of ductal adenocarcinoma (n=19), adenosquamous carcinoma (n=2) and mixed ductal-neuroendocrine carcinoma (n=1). Postoperatively, three patients died. The mean follow-up period was 17 months (2-54 months). Local recurrence of the tumour occurred in five cases, liver metastases in two cases and only one patient had pulmonary metastases. The other patients are still being followed-up. Conclusion: Ductal adenocarcinoma of the pancreas is associated with a high rate of mortality because of early invasion, widespread metastasis and lack of effective therapeutic modalities. Accurate diagnosis and staging of these tumours is critical for optimal treatment planning and for determining prognosis.

**Key words:** exocrine pancreas; ductal adenocarcinoma, pancreatic neoplasms, pathology.

## 1. INTRODUCTION

Pancreatic ductal adenocarcinoma is the deadliest solid cancer and currently the fourth most frequent cause of cancer related deaths (Vincent et al., 2011). Pancreatic ductal adenocarcinoma accounts for 85-90% of all pancreatic tumours (Hurban et al., 2010). It is characterized by late diagnosis due to lack of early symptoms, extensive metastasis, and high resistance to chemotherapy and radiation. In this paper, we report our experience with ductal adenocarcinoma of the pancreas and its variants over the past 14 years. Our aim was to analyze clinicopathological features, treatment and outcomes of 22 Tunisian patients who were surgically treated at our institution.

## 2. METHODS

We undertook a retrospective study of 22 patients who were operated on for ductal adenocarcinoma of the pancreas at the General Surgery Department of Mongi Slim hospital of Tunis between January 2000 and December 2013. The total number of cases of ductal adenocarcinoma of the pancreas and its variants diagnosed during the same period was 28. Six cases were excluded from this study because clinical data were lacking. The cases were retrieved from the files of the registry of surgery of the same hospital. Medical records were scrutinized for epidemiologic characteristics, predisposing factors, initial manifestations of the disease, methods of diagnosis, laboratory findings, surgical or palliative therapy and overall morbidity and mortality. Diagnosis of ductal adenocarcinoma was based upon clinical, imaging and histopathologic findings. All patients underwent imaging evaluation during the preoperative period. All specimens were surgically obtained. Tissues were fixed in 10% phosphate buffered formaldehyde, embedded in paraffin and sections were prepared for routine light microscopy after staining with hematoxylin and eosin. Immunohistochemical analysis was performed using the avidin-biotin complex technique with antibodies against cytokeratins 7 and 19, chromogranin A and synaptophysin. Patient confidentiality was maintained. Tumours were staged according to the International Union against Cancer (UICC) tumour-node-metastasis (TNM) classification system (7<sup>th</sup> edition).

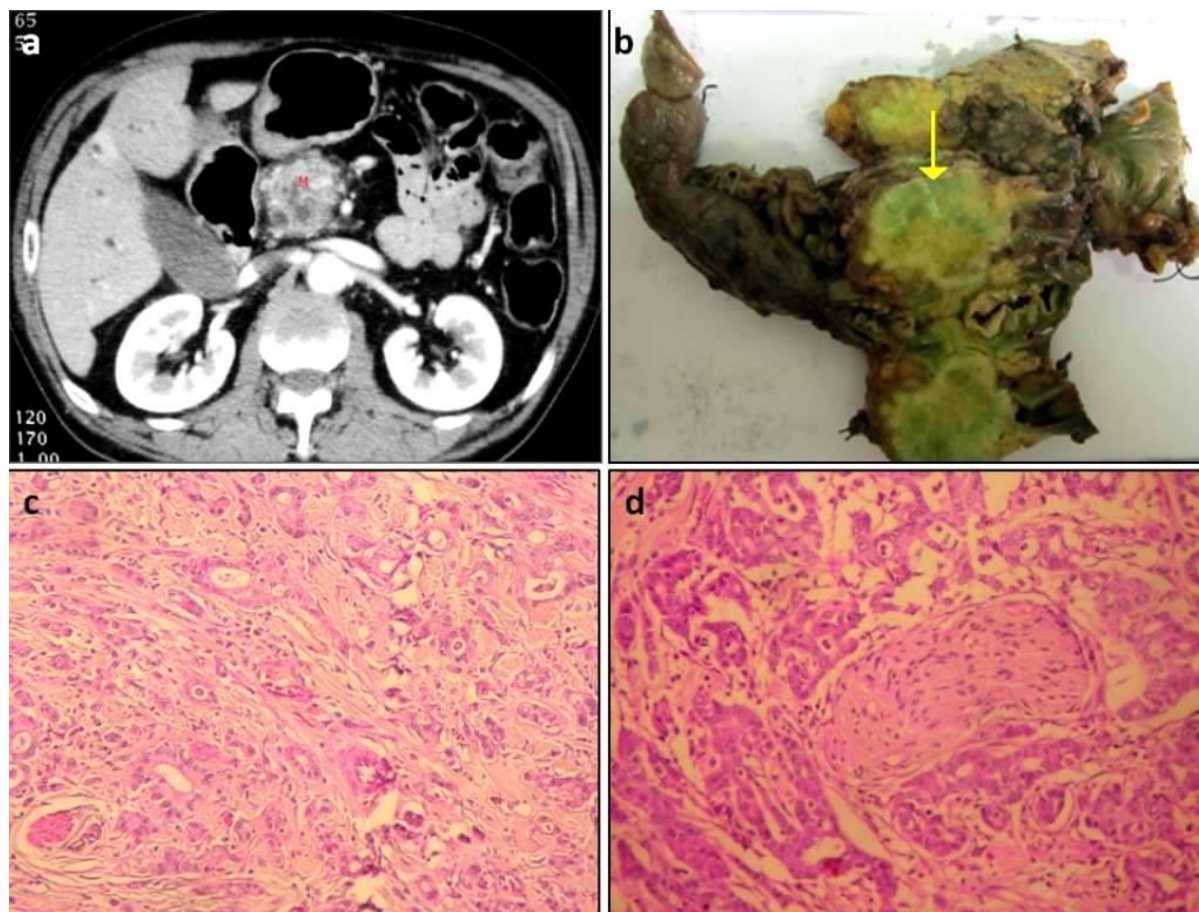
## 3. RESULTS

### Clinical findings

Our study group included 16 male and 6 female patients (sex-ratio M/F = 2,66) between 33 and 79 years of age (mean = 64,8 years). Thirteen patients were tobacco smokers and nine patients were alcoholic. Three patients were diabetic. Only one patient had a family history of pancreatic cancer. The presenting clinical symptoms were dominated by jaundice (n=21), followed by abdominal pain (n=18), altered general health (n=15), vomiting (n=3) and epigastralgia (n=3).

### Biological tests

Preoperative serum carbohydrate antigen (CA) 19-9 levels were performed in 20 cases. They were elevated in 18 cases (> 100 U/ml) and within normal range in two cases. Preoperative serum CEA levels were performed in 19 cases. They were elevated in 17 cases (> 5ng /ml) and within normal range in two cases.



**Figure 1** Radiological and pathological findings of ductal adenocarcinoma of the pancreas; **(a)** Abdominal computed tomography scan demonstrating a hypodense solid mass (\*M) of the pancreatic body with irregular contours and heterogeneous enhancement; **(b)** Macroscopic findings of infiltrating ductal adenocarcinoma. Ill-defined solid mass of the pancreatic head (arrow); **(c)** Moderately differentiated ductal adenocarcinoma. Haphazardly arranged infiltrating duct-like structures and medium sized neoplastic glands within a desmoplastic stroma. (Haematoxylin and eosin, magnification  $\times 200$ ); **(d)** Infiltrating ductal adenocarcinoma with perineural invasion (Haematoxylin and eosin, magnification  $\times 200$ ).

### Radiological findings

Diagnostic imaging techniques included abdominal ultrasonography (n=22), abdominal CT scan (n=22) and abdominal MRI (n=2). On CT scan, ductal adenocarcinomas were hypodense in 19 cases (Fig. 1a) and isodense in three cases. Dilatation of the pancreatic ducts was demonstrated in 10 cases. Dilatation of both the biliary and pancreatic ducts was noted in three cases. Twelve tumours demonstrated heterogeneous enhancement on contrast CT scan, whereas the remaining tumours did not show enhancement.

### Treatment

All patients underwent surgical treatment. Twenty patients underwent cephalic duodenopancreatectomy and two patients had total duodenopancreatectomy. Only two patients received adjuvant chemotherapy.

### Pathologic findings

#### Macroscopic findings

In our series, the tumours ranged in size from 1,5 to 6 cm (mean = 3,06 cm). The tumour was located in the head of the pancreas in 20 cases and in the body of the pancreas in two cases. On cut section, all tumours were firm sclerotic and poorly defined. They were gray-white to tan (n=14), yellowish (n= 6) or greenish (n= 2) (Fig.1b).

### Microscopic findings

Histopathological examination of the surgical specimen revealed that 19 cases were ductal adenocarcinomas with variable degrees of differentiation (well differentiated (n=7), moderately differentiated (n=10) (Fig.1c) and poorly differentiated (n=2)). There were two cases of adenosquamous carcinoma (in which the squamous component accounted for more than 30% of the neoplasm) and one case of mixed ductal-neuroendocrine carcinoma (characterized by an intimate admixture of neoplastic ductal and neoplastic neuroendocrine cells). Most ductal adenocarcinomas had a tubular pattern of growth with occasional acinar or cord-like pattern. The neoplastic cells were medium-sized, cuboidal or columnar with a small nuclei and eosinophilic cytoplasm. The stroma was desmoplastic and abundant in all cases. Pancreatic intra-epithelial neoplasia was detected in ten cases (PanIN1 (n=3), PanIN2 (n=3) and PanIN3 (n=4)). Perineural invasion was found in 17 cases (Fig.1d) and vascular invasion in 13 cases. Lymph node metastases were histologically detected in 17 cases. Upstream obstructive chronic pancreatitis was found in 12 cases.

### Immunohistochemistry

In our series, immunohistochemical study was performed in only one case. On immunohistochemistry, cytokeratins 7 and 19 were positive in the ductal component and negative in the neuroendocrine component; while chromogranin A and synaptophysin were positive in the neuroendocrine component and negative in the ductal component. Both the ductal and the neuroendocrine components comprised approximately 50% of the tumour. A diagnosis of mixed ductal-endocrine carcinoma was therefore established in this case.

### Staging according to UICC (7<sup>th</sup> edition)

In our series, ductal adenocarcinomas and its variants were classified after surgery as stage pT2N1M0 (n=2), pT3N0M0 (n=5) and pT3N1M0 (n=15).

### Operative morbidity and postoperative complications

Three patients with ductal adenocarcinoma died on postoperative day 1. Other postoperative complications included pancreatic fistula (n=8), hemorrhagic shock (n=4), peritonitis (n=5) and sepsis (n=2).

### Follow-up and evolution

The mean follow-up period of our patients was 17 months (range: 2 - 54 months). Three patients were lost to follow-up. Four patients died after a mean follow-up period of 10 months. Local recurrence of the tumour occurred in three cases, liver metastases in two cases six months postoperatively, peritoneal carcinomatosis in five cases 12 months postoperatively and one patient had pulmonary metastases four years postoperatively. The other patients are still being followed-up.

## 4. DISCUSSION

Pancreatic cancer usually refers to ductal adenocarcinomas of the pancreas, because more than 90% of pancreatic tumours arise from the ductal epithelium. Other major tumours of the pancreas include neuroendocrine malignancies, lymphomas and a variety of rare sarcomas (Hurban et al., 2010). In Tunisia, pancreatic cancer ranks 5<sup>th</sup> among digestive cancers with an incidence which varies between 1,45 and 2,9 per 100000 inhabitants per year (Ministère P et al., 2006). Most patients are between 60 and 80 years of age. The 2014 Surveillance Epidemiology and End Results (SEER) data indicate that the number of new cases and incidence rates in men (23,530) and women (22,890) are nearly equal (Maisonneuve P et al., 2015). Cigarette smoking is the leading environmental cause of pancreatic ductal adenocarcinoma, accounting for 25 to 35% of cases. Other risk factors include nutritional and dietary factors, chronic pancreatitis, diabetes mellitus, genetic syndromes, family history of pancreatic cancer and gastrectomy (Hurban et al., 2010, Siegel et al., 2014). In our series, 13 patients were tobacco smokers, three patients were diabetic and only one patient had a family history of pancreatic cancer. Pancreatic carcinoma is also characterized by multiple germline and somatic genetic mutations (Hurban et al., 1998). The *KRAS* oncogene, is the most frequently mutated oncogene in pancreatic cancer in (>90% of tumours) (Hurban et al., 2010). The tumour suppressor *CDKN2A/TP16*, a cell cycle control gene, is commonly inactivated in pancreatic cancer, with 80 to 95% loss of activity leading to increased cell cycle progression (Hurban et al., 2010).. Mutations in *TP53* are commonly found in 50 to 75% of pancreatic tumours. Inactivation of *SMAD4* (DPC4) is observed in over 50% of pancreatic cancers and is associated with worse prognosis and the development of metastases (Bartsch et al., 2004, Tersmette et al., 2001). Inactivation of *RB1* (in < 10% of pancreatic cancers) and *STK11* is also observed (Bartsch et al., 2004, Tersmette et al., 2001). Levels of CEA and CA 19-9 have been widely described to be elevated in up to 85% of the patients with pancreatic ductal adenocarcinoma (Duraket et al., 2007). CEA and CA 19-9 can predict survival after pancreatic resection and are markers for recurrent disease after curative resection of a pancreatic

ductal adenocarcinoma (Duraket et al., 2007). Specificity of CEA and CA 19-9 for pancreatic ductal adenocarcinoma ranges between 90 and 100%. In our series, preoperative serum carbohydrate antigen CA 19-9 levels were performed in 20 cases. They were elevated in 18 cases ( $> 100$  U/ml) and within normal range in two cases. Preoperative serum CEA levels were performed in 19 cases. They were elevated in 17 cases ( $> 5$  ng/ml) and within normal range in two cases. Because the pancreas is located deep within the retroperitoneum, clinical symptoms typically do not manifest until tumour has involved local vessels, caused perineural infiltration, or in pancreatic head tumours, biliary obstruction. Therefore, patients usually present with jaundice, weight loss, and/or abdominal pain (Modolell et al., 1999). Tumours of the pancreatic head, neck, and sometimes, the body often obstruct the common bile duct, causing jaundice. Tumours in the pancreatic tail often cause left-sided pain, whereas those in the pancreatic body often manifest with midepigastic pain (Kelsen et al., 1997). Other symptoms include fatigue, new-onset diabetes and steatorrhea related to pancreatic insufficiency (Kelsen et al., 1997). In our series, the presenting clinical symptoms were dominated by jaundice ( $n=21$ ), followed by abdominal pain ( $n=18$ ), altered general health ( $n=15$ ), vomiting ( $n=3$ ) and epigastralgia ( $n=3$ ). Imaging studies provide crucial information for accurately staging patients, assessing treatment response, detecting tumour recurrence and identifying complications. On CT scan, the tumour usually appears hypodense compared with the background parenchyma and borders whereas poorly defined lesions may be isoattenuating. Dilation of the upstream pancreatic duct and common bile duct is seen when the tumour is located within the pancreatic head. Pathology is generally regarded as the backbone of diagnoses in patients with pancreatic ductal adenocarcinoma (Verbeke et al., 2016). According to current best practice, a pathology report should confirm the diagnosis of pancreatic ductal adenocarcinoma and exclude other disease, provide the pT, pN-stage and additional descriptors such as margin status and, if applicable, evaluate tumour regression after neoadjuvant treatment (Verbeke et al., 2016). Morphological variation of pancreatic ductal adenocarcinoma is to some extent reflected in the WHO classification by the inclusion of so-called variants and patterns of ductal adenocarcinoma (Bartsch et al., 2004). Variants of ductal adenocarcinoma do not only exhibit a distinct morphological appearance, but differ also prognostically and may have a different molecular signature (Reid et al., 2014). Variants of ductal adenocarcinoma include adenosquamous, colloid, signet ring cell, medullary, hepatoid and undifferentiated carcinoma with or without osteoclast-like giant cells. Adenosquamous carcinoma is a rare pancreatic cancer that has been suggested to be distinct from pancreatic ductal adenocarcinoma both histopathologically and clinically (Hsu et al., 2008). Histologically, adenosquamous carcinoma is distinguished from ductal adenocarcinoma by the presence of both adenocarcinomatous and squamous components (more than 30% of the neoplasm). Clinically, the disease has been characterized by an extremely poor prognosis, even relative to that of ductal adenocarcinoma (Hsu et al., 2008). In our series, there were two cases of pancreatic adenosquamous carcinoma. Mixed pancreatic ductal neuroendocrine neoplasms are extremely rare and may have a more aggressive prognosis compared to pure neuroendocrine neoplasms due to the presence of a significant component of ductal adenocarcinoma (Hirano et al., 2011). Patients with mixed ductal-neuroendocrine carcinoma are usually older adults and present with nonspecific symptoms (Hirano et al., 2011). This neoplasm is characterized by an intimate admixture of neoplastic ductal and neoplastic neuroendocrine cells in the primary neoplasm as well as in its metastases. By definition, each component should comprise at least one third of the neoplastic tissue. Surgery offers the only chance for a cure for pancreatic ductal adenocarcinoma; however, 80% of patients are considered to be inoperable at diagnosis. No curative treatment is available for advanced stages of the disease. Adjuvant chemotherapies or chemo radiotherapies with 5-FU, gemcitabine, cisplatin, interferon alfa2b, or erlotinib have successfully reduced tumours or prolonged prognosis, but the beneficial effects of these treatments are limited (Neoptolemos et al., 2010). Even after surgery, the five-year survival rates for pancreatic ductal adenocarcinoma remain low, ranging from 15-20%, with most patients dying due to metastatic disease or local recurrence (Ahrendt et al., 2002). In our series, four patients died after a mean follow-up period of 10 months. Local recurrence of the tumour occurred in three cases, liver metastases in two cases, peritoneal carcinomatosis in five cases and one patient had pulmonary metastases four years postoperatively.

In summary, this retrospective study from Tunisia provides an overview on clinical symptoms, radiological features, treatment and outcome in 22 patients with ductal adenocarcinoma and its rare variants. Accurate diagnosis and staging of these tumours is critical for optimal treatment planning and for determining prognosis. With the increasing knowledge of the molecular pathogenesis of this disease, there is hope for nonsurgical alternatives in the future, especially targeted therapies. With limited advances in the treatment of advanced pancreatic ductal adenocarcinoma, the main hope for improved patient survival and potential cure lies in early detection of the disease when complete surgical resection is feasible and in supplementation with more effective therapeutic agents.

### Conflicts of interests

The authors declare no conflicts of interests.



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